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A synergistic activity of Hsp90 inhibitors and anticancer drugs in MIA PaCa-2 cell line

Recent studies show that Hsp90 inhibitors in combination with clinically used chemotherapeutic agents may act synergistically, therefore such effect can reduce the dose and toxicity of used drugs, and minimize or delay the induction of drug resistance [1].

The aim of our study was to evaluate activity of different combinations of two Hsp90 inhibitors (ICPD47 and ICPD62) and three anticancer agents (gemcitabine, 5-fluorouracil and doxorubicin) against pancreatic cancer cells. The effect of Hsp90 inhibitors, other agents and different combinations on cell viability was evaluated by MTT assay in MIA PaCa-2 cell line. The type of combination effect was determined by calculating combination index (CI), using CompuSyn software based on Chou-Talalay method [2]. Synergism was considered when CI < 1, antagonism when CI > 1, and CI value of 1 defined an additive effect of the drug combination. Also, 3D cell cultures were formed using 3D Bioprinting method and the activity of separate compounds and their combinations was examined by measuring the size change of spheroids.

Results. Among tested Hsp90 inhibitors ICPD62 had the greater effect on cell viability (EC50 value after 72 h was 0.446 ± 0.06 μM) and among anticancer agents doxorubicin showed the strongest effect on cell viability (EC50 value after 72 h was 0.076 ± 0.03 μM). Most of the combinations of Hsp90 inhibitors and anticancer agents with EC50 ratio 1:5 showed synergism (CI < 1, when fa = 0.5). The combination of ICPD47 and Gem demonstrated greatest synergistic activity (CI = 0.193, when fa = 0.5). In 3D cultures the combination of ICPD47 and 5-FU showed the strongest effect on spheroid growth, the size of the spheroid decreased by 37 % comparing to control group, which size decreased by 14 %.

Conclusion. The combination of Hsp90 inhibitors and Gem demonstrate the strongest synergistic anticancer activity in 2D models, and the combination of ICPD47 and 5-FU in 3D models of MIA PaCa-2 pancreatic cancer cell line, and may be worthy of further studies.